REVIEW

Hox genes and evolution [version 1; peer review: 3 approved]

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Abstract

Hox proteins are a deeply conserved group of transcription factors originally defined for their critical roles in governing segmental identity along the antero-posterior (AP) axis in *Drosophila*. Over the last 30 years, numerous data generated in evolutionarily diverse taxa have clearly shown that changes in the expression patterns of these genes are closely associated with the regionalization of the AP axis, suggesting that *Hox* genes have played a critical role in the evolution of novel body plans within Bilateria. Despite this deep functional conservation and the importance of these genes in AP patterning, key questions remain regarding many aspects of *Hox* biology. In this commentary, we highlight recent reports that have provided novel insight into the origins of the mammalian *Hox* cluster, the role of *Hox* genes in the generation of a limbless body plan, and a novel putative mechanism in which *Hox* genes may encode specificity along the AP axis. Although the data discussed here offer a fresh perspective, it is clear that there is still much to learn about *Hox* biology and the roles it has played in the evolution of the Bilaterian body plan.

Keywords

homeobox , AP patterning , hox function , regionalization , deregionalized

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Introduction

Hox proteins are a group of homeodomain-containing transcription factors that are renowned for their roles in patterning animal body plans and for their remarkably deep evolutionary conservation. Homeodomain proteins are defined by the presence of a highly conserved DNA-binding region known as the homeodomain and are encoded by Homeobox genes. In general, homeobox genes are a large family of similar genes and can be divided into 11 different gene classes in animals, and the *Hox* genes belong to the ANTP class^{1,2}. This class of genes also includes the closely related ParaHox genes, NK genes, and various others. It has been suggested that the evolution and expansion of *Hox* genes have played a key role in the rapid diversification of the body plans of all Bilaterians. Thus, this group of genes has fascinated evolutionary biologists for decades and continues to be studied by many research groups today.

Hox genes were originally discovered in *Drosophila* and functional studies in the fly showed that these genes play a critical role in establishing segmental identity along the antero-posterior (AP) axis³. Subsequent analyses have shown that the role of *Hox* genes in establishing AP axis identity is conserved in vertebrates⁴⁻⁶. These data were very exciting and confirmed that their function was conserved in evolutionarily distant taxa. Since their original discovery in the fly over 30 years ago, *Hox* genes have now been cloned and analyzed in a wide array of animal groups ranging from hydra to humans. Collectively, these studies have provided key insights into the evolutionary origins of *Hox* genes and have reinforced the important role these genes have played in the evolution of Bilaterian body plans.

In this review, we provide a commentary on the recent advances on the origin, functional conservation, and regulative properties of *Hox* genes. The purpose of this review is not to provide a comprehensive detailed survey of the literature to date but rather to highlight recent data that have both challenged traditional views and enhanced our understanding of *Hox* genes and evolution.

Evolution of the Hox genes

None of the ANTP class of homeobox genes (including the *Hox* genes) is found outside of the metazoans². During the evolution of metazoans, the sponges diverged first, followed by cnidarians (jellyfish and corals), and both of these groups are more basal to the Bilaterians. Analysis of whole genome information from the demosponge *Amphimedon queenslandica* revealed the first conclusive evidence that sponges have several NK homeobox genes but do not have any definitive *Hox* or ParaHox genes⁷. In contrast, definitive *Hox*-like genes have been identified in the Cnidarians; however, the expression patterns of these genes do not follow a clear AP pattern or show any correlation with the Bilaterian *Hox* code in determining axis specification⁸. Phylogenetic analyses of ANTP class genes have shown that the *Hox* and ParaHox genes are more closely related to each other than they are to the NK subclass^{1,7}. Therefore, the current collection of genomic and phylogenetic data support the hypothesis that the NK, *Hox*, and ParaHox genes arose prior to the emergence of Bilaterian animals. Furthermore, it has been proposed that all three gene subclasses are derived from a hypothetical ancestral ANTP class gene that underwent

extensive tandem gene duplications that ultimately created the three distinct gene clusters¹. Interestingly, each of these three gene clusters has been conserved to different extents in various evolutionary lineages within Bilateria^{1,8}. For example, vertebrates have tightly linked *Hox* and ParaHox clusters and disrupted NK clusters, whereas dipterans (including *Drosophila*) exhibit a disrupted *Hox* cluster but have retained a tight NK cluster¹. Despite these differences, the birth and diversification of ANTP class genes have been instrumental in the evolution of the Bilaterian body plan and have contributed to the subsequent radiation of these animal taxa into nearly every ecological niche on earth.

Typically, invertebrates possess a single *Hox* cluster, whereas vertebrates possess multiple clusters that differ among different taxa⁹. For example, mammalian genomes have four *Hox* clusters whereas teleost fishes have up to eight *Hox* clusters⁹⁻¹¹. Although *Hox* genes and clusters are relatively well characterized in most vertebrates, the evolution of these genes within this group remains largely obscure because of the incompletely resolved phylogenetic history of these genes¹². In particular, the evolutionary origins of the *Hox*-bearing chromosomes in mammals remain highly controversial. The classic view is that the four clusters of *Hox* genes in humans originated through two rounds of whole genome duplications¹³⁻¹⁵. However, over the past few years, with the rapidly increasing availability of high-quality whole genome sequence data from a variety of animal species, the evolutionary history and organization of mammalian *Hox* genes have been subjected to rigorous scrutiny^{12,16-20}. Analyses of these emerging genomic datasets with advanced phylogenetic techniques have generated data that are inconsistent with the whole genome duplication hypothesis and instead favor the hypothesis that the configuration of *Hox*-bearing chromosomes in mammals may have resulted from small-scale events early in vertebrate evolution that include segmental duplications, independent gene duplication, and translocations¹². Such advanced phylogenetic techniques will continue to prove valuable and will provide more rigorous analyses of the evolution of the *Hox* genes as more high-quality whole genome sequence data from more basal metazoan taxa become available.

Conservation of Hox function in antero-posterior patterning

The spatial and temporal expression patterns of *Hox* genes along the AP axis of flies reflect their position on the chromosome: genes at the most 3' end are expressed earlier in development in more anterior parts of the embryo, and genes at the more 5' position are expressed later in development in more posterior regions of the embryo⁹. Studies in mice have shown the spatial and temporal expression patterns of these genes are also correlated with their position from 3' to 5' in each cluster, indicating that the spatial and temporal collinearity of the *Hox* genes is conserved in mammals^{4-6,21}. To date, *Hox* gene expression analyses in the vertebral column have been extended into several vertebrate taxa, including teleost fishes²², squamates^{4,23-25}, and archosaurs^{4,26,27}. Comparative analyses of the *Hox* code in several amniote taxa provide strong evidence that the evolutionary differences in the axial skeleton correspond to changes in the expression domains of *Hox* genes²⁶. As more diverse taxa are sampled, the trend of deep conservation of the spatio-temporal expression and function of the

Hox genes along the AP axis seems to be continually reinforced and underlies the critical roles that these genes have played in the evolution of the Bilaterian body plan.

There is an overwhelming amount of data that support that *Hox* genes are critical for patterning the axial skeleton in vertebrates and that changes in *Hox* gene expression have helped shape the evolution of novel body plans within Bilateria^{4,5}. With these cumulative results, the origin of the snake-like body plan (as well as other snake-like squamates) with its “deregalionalized” axial skeleton^{28,29} has been an intriguing evolutionary feature that has received considerable attention over the last decade with regard to *Hox* gene expression and function^{23,25,28–30}. In limbed lizards, two distinct regional boundaries are observed in the axial skeleton: the cervical-thoracic and the thoracic-lumbar, both of which have been shown to correspond to sharp boundaries of differential *Hox* gene expression patterns^{23,25,28}. In contrast, it has been reported that the snake-like body plan lacks clear boundaries, resulting in a “deregalionalized” axial skeleton with an increased number of vertebra and ribs and a reduction or loss of limbs and sternum^{28,29}. Previous studies in mice have shown that the inactivation of all three genes in the *Hox10* paralogous group (*Hoxa10*, *Hoxc10*, and *Hoxd10*) results in the transformation of the ribless lumbar vertebrae into a posterior extension of the thorax, as defined by the presence of ectopic ribs^{31,32}. These and many other genetic studies demonstrate that the activity of the genes in the *Hox10* paralogous group controls key processes in somatic patterning that lead to the inhibition of rib development. However, expression analyses in snake embryos have shown that both *Hoxa10* and *Hoxc10* are expressed in rib-bearing regions of the axial skeleton, suggesting the possibility that snake *Hoxa10* and *Hoxc10* genes have lost the ability to suppress rib-bearing vertebrae^{25,30}. Generation of transgenic mice that ectopically express snake *Hoxa10* showed that this paralog is able to efficiently block rib formation in mice, indicating that rib-repressing properties are still present in the snake protein³³. Instead, a polymorphism was identified in a *Hox/Pax*-responsive enhancer that is involved in *Hox*-mediated regulation of rib formation, which results in this enhancer being unable to respond to *Hox10* proteins³³. In addition, this polymorphism was also found in other animals with extended rib cages. These data indicate that the evolution of this *Hox/Pax* enhancer has played a critical role in the evolution of axial skeletons by modulating responses to either rib-suppressing or rib-promoting *Hox* genes.

A recent report that more closely analyzed the morphological differences of snake vertebrae has challenged the traditional view that the anterior axial skeleton of snakes is, in fact, “deregalionalized”²⁸. Using a statistical geometric morphometric analysis on the vertebral morphology, Head and Polly²⁸ concluded that there was no consistent difference in the shape variance between limbed and snake-like squamates and that three to four distinct vertebral regions, including the cervical, thoracic, and lumbar regions, could be identified in all taxa irrespectively of the presence or absence of limbs. In other words, snake-like body plans do indeed have regionalized precloacal axial skeletons; the differences in the morphologies of the vertebrae are just more subtle as compared with limbed reptiles. In addition, the authors asserted that the newly

identified morphological boundaries of the snake vertebral columns correspond to similar mapped expression boundaries of *Hox* paralogs in snakes, suggesting that the AP axis of these animals is governed by a normally functioning *Hox* code.

From an evolutionary perspective, the “deregalionalization” of the snake axial skeleton made the assumption that this body plan evolved from an ancestor that exhibited a regionalized AP vertebral axis. The new data reported in Head and Polly challenge this assumption and instead suggest that the regionalized axial skeletons of limbed reptiles and other derived vertebrate taxa are descended from an axial plan that displayed very little regionalization in the first place²⁸. Indeed, this hypothesis is supported by acquired fossil evidence from Paleozoic amniotes, including extinct stem members of Reptilia and Mammalia, that shows that these animals exhibited “deregalionalized” axial skeletons with very subtle changes in their primaxial morphology²⁸. These data support a model wherein regionalized vertebral columns (including the ones in snakes) are a derived feature that has arisen through modifications of a more “deregalionalized” ancestral body plan. In this case, the evolution of the snake-like body plan is not an exception but rather just another example along the continuum of *Hox* function in sculpting derived body plans in the diverse Bilaterian taxa.

In addition to their highly conserved roles in AP patterning, numerous studies have indicated that *Hox* genes have been co-opted for novel functions in the development of many organ systems. For example, previous studies have shown that the expression patterns of the *Hox* gene *Ultrabithorax* (*Ubx*) are associated with the differential enlargement of particular hind-limb segments in different insect species^{34,35}. In a similar fashion, the *Hox* gene *Abdominal-B* is required for the formation of the lantern organ on the posterior abdomen in the firefly³⁶. Although studies in insects are informative, our most comprehensive understanding of co-opted *Hox* gene functions comes from studies in mice. These studies have identified several important roles for *Hox* genes in the development of organs that correspond to their expression along the AP axis. Some of the many examples include the following: the *Hox3* genes in the development of the thymus, thyroid, and parathyroid^{37,38}; *Hox5* genes in lung development^{39,40}; *Hox6* genes in pancreas development⁴¹; *Hox9*, *Hox10*, and *Hox11* genes in the reproductive tract^{42–46}; *Hox10* and *Hox11* genes in kidney development^{47–49}; and *Hoxb13* gene for prostate development⁵⁰. Although *Hox* genes have been shown to play important roles in many aspects of organogenesis, it has been difficult to place these highly conserved transcription factors into established regulatory networks. This represents an important gap in our understanding of *Hox* biology that needs to be addressed in much greater detail.

It has been well established that the diversity along the AP axis of animals results from the differential expression of *Hox* genes, which in turn regulate different sets of target genes that govern the formation of anatomical regions that have specific features⁵¹. However, how *Hox* genes encode this specificity has been a long-debated question. All *Hox* proteins have similar DNA-binding domains (the homeodomain) and they all bind similar DNA sequences with high affinity^{51–56}. One well-established means

by which *Hox* genes achieve specificity *in vivo* is to bind DNA co-operatively with other DNA-binding co-factors^{55,57}. To date, the three amino acid loop extension (TALE)-homeodomain genes, which include the PBC/PBX and MEIS classes of homeodomain proteins, are the best described co-factors; however, it is clear that others exist^{55,57–61}. The PBC/PBX class comprises fly Extradenticle (Exd) and vertebrate Pbx homeoproteins, whereas the MEIS class includes fly Homothorax (Hth) and vertebrate Meis and Prep homeoproteins⁵⁷. In addition to the presence or absence of co-factors, a recent report has significantly contributed to additional understanding of how *Hox* genes encode specificity in *Drosophila*⁵⁴. Briefly, these researchers identified clusters of low-affinity binding sites in enhancers of the *shavenbaby* (*svb*) gene that specifically confer binding of an Ubx-Exd complex. Mutation of these sites into high-affinity sites enabled the enhancer to respond to other *Hox* genes (*Scr*), suggesting that the native low-affinity Ubx-Exd binding sites confer specificity for Ubx-Exd dimers over other Hox proteins and probably over other homeodomain proteins as well. Interestingly, although the individual Ubx binding sites were not conserved in another fly species (*Drosophila virilis*), clusters of other low-affinity binding sites were identified and found to be required for enhancer function, suggesting that this mechanism may be an evolutionarily conserved strategy used by *svb* enhancers. Determining whether similar mechanisms convey *Hox* specificity in more derived Bilaterian species will be particularly informative and will provide insight into whether this mechanism is a highly conserved feature.

Future directions

The remarkably deep conservation of *Hox* gene organization and function and their profound impact on the evolution of metazoan body plans continue to fascinate evolutionary and developmental biologists today. As a result, *Hox* genes continue to be investigated by a large number of research groups. The focus of these studies encompasses many different aspects of *Hox* biology, including *Hox* gene regulation, identification of downstream targets, and uncovering novel functions for these proteins. In addition, *Hox* genes have been associated with a number of human diseases⁶² and this in turn supports an increased need to understand the potential role(s) of these genes in the onset and progression of disease. Finally, functional roles of *Hox* genes have also been identified during postnatal development^{63–65}, and there is increasing interest in understanding the roles that these genes play in the formation of post-embryonically derived structures and the maintenance of organ systems. There remains much more to learn about *Hox* gene biology and thus it is certain that these genes will continue to fascinate investigators for decades to come.

Competing interests

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References

- Holland PW: Did homeobox gene duplications contribute to the Cambrian explosion? *Zoological Lett.* 2015; 1: 1.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Holland PW: Evolution of homeobox genes. *Wiley Interdiscip Rev Dev Biol.* 2013; 2(1): 31–45.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Lewis EB: A gene complex controlling segmentation in *Drosophila*. *Nature.* 1978; 276(5688): 565–70.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Burke AC, Nelson CE, Morgan BA, et al.: Hox genes and the evolution of vertebrate axial morphology. *Development.* 1995; 121(2): 333–46.
[PubMed Abstract](#)
- Mallo M, Wellik DM, Deschamps J: Hox genes and regional patterning of the vertebrate body plan. *Dev Biol.* 2010; 344(1): 7–15.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Wellik DM: Hox patterning of the vertebrate axial skeleton. *Dev Dyn.* 2007; 236(9): 2454–63.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Larroux C, Fahey B, Degnan SM, et al.: The NK homeobox gene cluster predates the origin of Hox genes. *Curr Biol.* 2007; 17(8): 706–10.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Reddy PC, Unni MK, Gungi A, et al.: Evolution of Hox-like genes in Cnidaria: Study of Hydra Hox repertoire reveals tailor-made Hox-code for Cnidarians. *Mech Dev.* 2015; 138(Pt 2): 87–96.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Pascual-Anaya J, D'Aniello S, Kuratani S, et al.: Evolution of Hox gene clusters in deuterostomes. *BMC Dev Biol.* 2013; 13: 26.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Hoegg S, Meyer A: Hox clusters as models for vertebrate genome evolution. *Trends Genet.* 2005; 21(8): 421–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Kuraku S, Meyer A: The evolution and maintenance of hox gene clusters in vertebrates and the teleost-specific genome duplication. *Int J Dev Biol.* 2009; 53(5–6): 765–73.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Abbasi AA: Diversification of four human Hox gene clusters by step-wise evolution rather than ancient whole-genome duplications. *Dev Genes Evol.* 2015; 225(6): 353–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Kasahara M: The 2R hypothesis: an update. *Curr Opin Immunol.* 2007; 19(5): 547–52.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Ohno S: Evolution by Gene Duplication. Berlin, Heidelberg: Springer Berlin Heidelberg, 1970.
[Publisher Full Text](#)
- Putnam NH, Butts T, Ferrier DE, et al.: The amphioxus genome and the evolution of the chordate karyotype. *Nature.* 2008; 453(7198): 1064–71.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Abbasi AA: Unraveling ancient segmental duplication events in human genome by phylogenetic analysis of multigene families residing on Hox-cluster paralogs. *Mol Phylogenet Evol.* 2010; 57(2): 836–48.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Abbasi AA, Grzeschik KH: An insight into the phylogenetic history of Hox linked gene families in vertebrates. *BMC Evol Biol.* 2007; 7: 239.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Ambreen S, Khalil F, Abbasi AA: Integrating large-scale phylogenetic datasets to dissect the ancient evolutionary history of vertebrate genome. *Mol Phylogenet Evol.* 2014; 78: 1–13.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Asrar Z, Haq F, Abbasi AA: Fourfold paralogy regions on human Hox-bearing chromosomes: role of ancient segmental duplications in the evolution of vertebrate genome. *Mol Phylogenet Evol.* 2013; 66(3): 737–47.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Hughes AL, da Silva J, Friedman R: Ancient genome duplications did not

- structure the human *Hox*-bearing chromosomes. *Genome Res.* 2001; 11(5): 771–80.
[PubMed Abstract](#) | [Free Full Text](#)
21. Duboule D, Dollé P: The structural and functional organization of the murine *Hox* gene family resembles that of *Drosophila* homeotic genes. *EMBO J.* 1989; 8(5): 1497–505.
[PubMed Abstract](#) | [Free Full Text](#)
 22. **F** Morin-Kensicki EM, Melancon E, Eisen JS: Segmental relationship between somites and vertebral column in zebrafish. *Development.* 2002; 129(16): 3851–60.
[PubMed Abstract](#) | [F1000 Recommendation](#)
 23. Cohn MJ, Tickle C: Developmental basis of limblessness and axial patterning in snakes. *Nature.* 1999; 399(6735): 474–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 24. Ohya YK, Kuraku S, Kuratani S: *Hox* code in embryos of Chinese soft-shelled turtle *Pelodiscus sinensis* correlates with the evolutionary innovation in the turtle. *J Exp Zool B Mol Dev Evol.* 2005; 304(2): 107–18.
[PubMed Abstract](#) | [Publisher Full Text](#)
 25. Woltering JM, Vonk FJ, Müller H, et al.: Axial patterning in snakes and caecilians: evidence for an alternative interpretation of the *Hox* code. *Dev Biol.* 2009; 332(1): 82–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 26. **F** Böhmer C, Rauhut OW, Wörheide G: New insights into the vertebral *Hox* code of archosaurs. *Evol Dev.* 2015; 17(5): 258–69.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 27. Mansfield JH, Abzhanov A: *Hox* expression in the American alligator and evolution of archosaurian axial patterning. *J Exp Zool B Mol Dev Evol.* 2010; 314(8): 629–44.
[PubMed Abstract](#) | [Publisher Full Text](#)
 28. **F** Head JJ, Polly PD: Evolution of the snake body form reveals homoplasy in amniote *Hox* gene function. *Nature.* 2015; 520(7545): 86–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 29. Woltering JM: From lizard to snake; behind the evolution of an extreme body plan. *Curr Genomics.* 2012; 13(4): 289–99.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 30. Di-Poi N, Montoya-Burgos JI, Miller H, et al.: Changes in *Hox* genes' structure and function during the evolution of the squamate body plan. *Nature.* 2010; 464(7285): 99–103.
[PubMed Abstract](#) | [Publisher Full Text](#)
 31. Carapuço M, Nóvoa A, Bobola N, et al.: *Hox* genes specify vertebral types in the presomitic mesoderm. *Genes Dev.* 2005; 19(18): 2116–21.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 32. Wellik DM, Capecchi MR: *Hox10* and *Hox11* genes are required to globally pattern the mammalian skeleton. *Science.* 2003; 301(5631): 363–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 33. **F** Guerreiro I, Nunes A, Woltering JM, et al.: Role of a polymorphism in a *Hox/Pax*-responsive enhancer in the evolution of the vertebrate spine. *Proc Natl Acad Sci U S A.* 2013; 110(26): 10682–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 34. **F** Mahfooz N, Turchyn N, Mihajlovic M, et al.: *Ubx* regulates differential enlargement and diversification of insect hind legs. *PLoS One.* 2007; 2(9): e866.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 35. Mahfooz NS, Li H, Popadić A: Differential expression patterns of the *Hox* gene are associated with differential growth of insect hind legs. *Proc Natl Acad Sci U S A.* 2004; 101(14): 4877–82.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 36. **F** Stansbury MS, Moczek AP: The function of *Hox* and appendage-patterning genes in the development of an evolutionary novelty, the *Photuris* firefly lantern. *Proc Biol Sci.* 2014; 281(1782): 20133333.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 37. Dollé P, Izpisua-Belmonte JC, Brown JM, et al.: *HOX-4* genes and the morphogenesis of mammalian genitalia. *Genes Dev.* 1991; 5(10): 1767–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 38. Manley NR, Capecchi MR: *Hox* group 3 paralogs regulate the development and migration of the thymus, thyroid, and parathyroid glands. *Dev Biol.* 1998; 195(1): 1–15.
[PubMed Abstract](#) | [Publisher Full Text](#)
 39. Boucherat O, Montaron S, Bérubé-Simard FA, et al.: Partial functional redundancy between *Hoxa5* and *Hoxb5* paralog genes during lung morphogenesis. *Am J Physiol Lung Cell Mol Physiol.* 2013; 304(12): L817–30.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 40. Hrycaj SM, Dye BR, Baker NC, et al.: *Hox5* Genes Regulate the *Wnt2/2b-Bmp4*-Signaling Axis during Lung Development. *Cell Rep.* 2015; 12(6): 903–12.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 41. Larsen BM, Hrycaj SM, Newman M, et al.: Mesenchymal *Hox6* function is required for mouse pancreatic endocrine cell differentiation. *Development.* 2015; 142(22): 3859–68.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 42. Benson GV, Lim H, Paria BC, et al.: Mechanisms of reduced fertility in *Hoxa-10* mutant mice: uterine homeosis and loss of maternal *Hoxa-10* expression. *Development.* 1996; 122(9): 2687–96.
[PubMed Abstract](#)
 43. Gendron RL, Paradis H, Hsieh-Li HM, et al.: Abnormal uterine stromal and glandular function associated with maternal reproductive defects in *Hoxa-11* null mice. *Biol Reprod.* 1997; 56(5): 1097–105.
[PubMed Abstract](#) | [Publisher Full Text](#)
 44. Podlasek CA, Seo RM, Clemens JQ, et al.: *Hoxa-10* deficient male mice exhibit abnormal development of the accessory sex organs. *Dev Dyn.* 1999; 214(1): 1–12.
[PubMed Abstract](#) | [Publisher Full Text](#)
 45. **F** Raines AM, Adam M, Magella B, et al.: Recombineering-based dissection of flanking and paralogous *Hox* gene functions in mouse reproductive tracts. *Development.* 2013; 140(14): 2942–52.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 46. Taylor HS, Vanden Heuvel GB, Igarashi P: A conserved *Hox* axis in the mouse and human female reproductive system: late establishment and persistent adult expression of the *Hoxa* cluster genes. *Biol Reprod.* 1997; 57(6): 1338–45.
[PubMed Abstract](#) | [Publisher Full Text](#)
 47. Schwab K, Hartman HA, Liang HC, et al.: Comprehensive microarray analysis of *Hoxa11/Hoxd11* mutant kidney development. *Dev Biol.* 2006; 293(2): 540–54.
[PubMed Abstract](#) | [Publisher Full Text](#)
 48. **F** Wellik DM, Hawkes PJ, Capecchi MR: *Hox11* paralogous genes are essential for metanephric kidney induction. *Genes Dev.* 2002; 16(11): 1423–32.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 49. Yallowitz AR, Hrycaj SM, Short KM, et al.: *Hox10* genes function in kidney development in the differentiation and integration of the cortical stroma. *PLoS One.* 2011; 6(8): e23410.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 50. Economides KD, Capecchi MR: *Hoxb13* is required for normal differentiation and secretory function of the ventral prostate. *Development.* 2003; 130(10): 2061–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 51. McGinnis W, Krumlauf R: Homeobox genes and axial patterning. *Cell.* 1992; 68(2): 283–302.
[PubMed Abstract](#) | [Publisher Full Text](#)
 52. Akam M: *Hox* and *HOM*: homologous gene clusters in insects and vertebrates. *Cell.* 1989; 57(3): 347–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 53. Berger MF, Badis G, Gehrke AR, et al.: Variation in homeodomain DNA binding revealed by high-resolution analysis of sequence preferences. *Cell.* 2008; 133(7): 1266–76.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 54. **F** Crocker J, Abe N, Rinaldi L, et al.: Low affinity binding site clusters confer *hox* specificity and regulatory robustness. *Cell.* 2015; 160(1–2): 191–203.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 55. Mann RS, Lelli KM, Joshi R: *Hox* specificity unique roles for cofactors and collaborators. *Curr Top Dev Biol.* 2009; 88: 63–101.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 56. **F** Noyes MB, Christensen RG, Wakabayashi A, et al.: Analysis of homeodomain specificities allows the family-wide prediction of preferred recognition sites. *Cell.* 2008; 133(7): 1277–89.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 57. Moens CB, Selli L: *Hox* cofactors in vertebrate development. *Dev Biol.* 2006; 291(2): 193–206.
[PubMed Abstract](#) | [Publisher Full Text](#)
 58. **F** Rezsöházy R, Saurin AJ, Maurel-Zaffran C, et al.: Cellular and molecular insights into *Hox* protein action. *Development.* 2015; 142(7): 1212–27.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 59. **F** Amin S, Donaldson IJ, Zannino DA, et al.: *Hoxa2* selectively enhances Meis binding to change a branchial arch ground state. *Dev Cell.* 2015; 32(3): 265–77.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 60. Gong KQ, Yallowitz AR, Sun H, et al.: A *Hox-Eya-Pax* complex regulates early kidney developmental gene expression. *Mol Cell Biol.* 2007; 27(21): 7661–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 61. Yallowitz AR, Gong KQ, Swinehart IT, et al.: Non-homeodomain regions of *Hox* proteins mediate activation versus repression of *Six2* via a single enhancer site *in vivo*. *Dev Biol.* 2009; 335(1): 156–65.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 62. Quinonez SC, Innis JW: Human *HOX* gene disorders. *Mol Genet Metab.* 2014; 111(1): 4–15.
[PubMed Abstract](#) | [Publisher Full Text](#)
 63. Mandeville I, Aubin J, LeBlanc M, et al.: Impact of the loss of *Hoxa5* function on lung alveogenesis. *Am J Pathol.* 2006; 169(4): 1312–27.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 64. Pineault KM, Swinehart IT, Garthus KN, et al.: *Hox11* genes regulate postnatal longitudinal bone growth and growth plate proliferation. *Biol Open.* 2015; 4(11): 1538–48.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 65. Morgan R: *Hox* genes: a continuation of embryonic patterning? *Trends Genet.* 2006; 22(2): 67–9.
[PubMed Abstract](#) | [Publisher Full Text](#)

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